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(54) Title: COMBINATIONS OF ANGIOSTATIC COMPOUNDS

(57) Abstract

The present invention is directed to compositions containing combinations of angiostatic compounds and methods for their use in preventing pathological neovascularization.

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COMBINATIONS OF ANGIOSTATIC COMPOUNDS

Background of the invention

The present invention relates to certain compounds useful in preventing and treating neovascularization. Specifically, the invention is directed to compositions containing two or more combinations of angiostatic agents and methods of using combinations of these angiostatic agents to treat neovascularization.

Angiogenesis is a term used to describe the development of new blood vessels or neovascularization (L. Diaz-Flores et al., *Angiogenesis: an Update*, Histology and Histopathology, volume 9, pages 807-843 (1994)). Though angiogenesis is a normal process for the development or maintenance of the vasculature, pathological conditions (i.e., angiogenesis dependent diseases) arise where blood vessel growth is actually harmful. Such pathologies include diabetic retinopathies, proliferative vitreoretinopathies, psoriasis, arthritis and solid tumor development. The progression of angiogenesis occurs in several phases which include: elaboration of the angiogenic signal; dissolution of the blood vessel basement membrane; endothelial cell proliferation; endothelial cell migration; and formation and differentiation of capillary tubules and loops. Each of these phases is a potential target for pharmacological intervention.

Tumor growth is dependent on neovascularization. For solid tumors to grow beyond the size of a pea, they must become vascularized. They do so by secreting their

own angiogenic factor(s) which recruit new blood vessels to provide essential nutrients and oxygen.

Angiogenesis is also associated with important diseases of ocular tissue especially in older patients and diabetics. Any abnormal growth of blood vessels in the eye can scatter and block the incident light prior to reaching the retina. Neovascularization can occur at almost any site in the eye and significantly alter ocular tissue function. Some of the most threatening ocular neovascular diseases are those which involve the retina. For example, many diabetic patients develop a retinopathy which is characterized by the formation of leaky, new blood vessels on the anterior surface of the retina and in the vitreous causing proliferative vitreoretinopathy. A subset of patients with age related macular degeneration develop subretinal neovascularization which leads to their eventual blindness.

Current therapy for the treatment of ocular neovascular disease is not very effective. Retinal neovascularization is often treated with multiple laser burns to the retina to remove the pathological vasculature. Panretinal photocoagulation, however, destroys normal retinal tissue. Patients with neovascular diseases of the anterior chamber (e.g. corneal neovascularization, iritis rubeosis) are treated with potent topical ocular glucocorticoids. These therapies are only partially effective and generally only slow neovascularization and the progress of the overall disease. In addition, they can cause severe side effects if used over a relatively long period of time.

Other attempts have been made to provide therapies for the prevention or treatment of pathological angiogenesis. For example, angiostatic steroids functioning to inhibit angiogenesis in the presence of heparin or specific heparin fragments in the

chicken embryo model of neovascularization are disclosed in Crum, et al., *A New Class of Steroids Inhibits Angiogenesis in the Presence of Heparin or a Heparin Fragment*, Science, volume 230, pages 1375-1378 (1985). Other groups of angiostatic steroids useful in inhibiting angiogenesis are disclosed in commonly assigned WIPO Publication No. WO 93/10141 (Clark et al.) and United States Patent No. 5,371,078 (Clark et al.), as well as WO 95/18621 (Prioa et al.).

Glucocorticoids, as mentioned above, have also been shown to inhibit angiogenesis. However, the use of glucocorticoid therapy in general is complicated by the inherent problems associated with steroid applications. Such problems include elevated intraocular pressure (Kitazawa, *Increased Intraocular Pressure Induced by Corticosteroids*, American Journal of Ophthalmology, volume 82, pages 492-495 (1976)), and the development of posterior subcapsular cataracts.

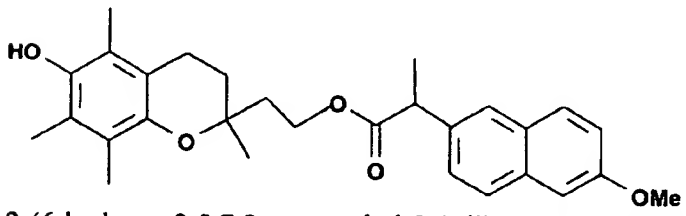
Suramin, a complex molecule, has been described as a growth factor antagonist and possessing angiosuppressive action (Takano, *Angiosuppressive and Antiproliferative Actions of Suramin: A Growth Factor Antagonist*, Growth Factors, Peptides and Receptors, Ed. T.W. Moody, Plenum Press, New York, pages 255-264 (1993)). Suramin and its derivatives have also been disclosed in WIPO Publication No. WO 90/15816, as inhibitors of fibroblast growth factor (an angiogenesis factor) as well as apparent angiostatic agents.

Fumagillin and analogs of fumagillin have been reported to possess angiostatic properties (Ingber et al., *Synthetic Analogues of Fumagillin that Inhibit Angiogenesis and Suppress Tumor Growth*, Nature, volume 348, pages 555-557 (1990)). Several European patent applications have disclosed fumagillin analogs including: European Patent

Activator In Bovine Endothelial Cells, volume 44, pages 859-864 (1989)) or by inhibiting PAI-1 synthesis (Blei et al., *Mechanism of Action of Angiostatic Steriods: Suppression of Plasminogen Activator Activity Via Stimulation of Plasminogen Activator Inhibitor Synthesis*, Journal of Cellular Physiology, volume 155, pages 568-578 (1993)). Therefore, therapeutic intervention is possible at several points in the process.

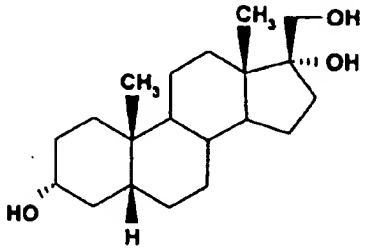
While applicants do not wish to be bound by any theory, it is believed that the inhibition of multiple cellular/biological mechanisms associated with angiogenesis will more effectively inhibit neovascularization. Therefore, the use of combinations of compounds affecting different mechanisms of angiogenesis would be more effective in preventing neovascularization than a single therapeutic approach. For example, combinations of anti-proliferative compounds such as chroman derivatives and angiostatic steroids which affect basement membrane breakdown would be more effective in preventing neovascularization than either drug alone. Therefore, the present invention sets forth the use of combinations of different angiostatic agents to provide a more effective therapeutic approach to inhibiting neovascularization. As used herein, the term "angiostatic agent or compound" refers to any compound which inhibits one or more processes of angiogenesis such that angiogenesis is inhibited or retarded.

Preferred compounds of formula (I), also known as "chroman derivatives," include the following:

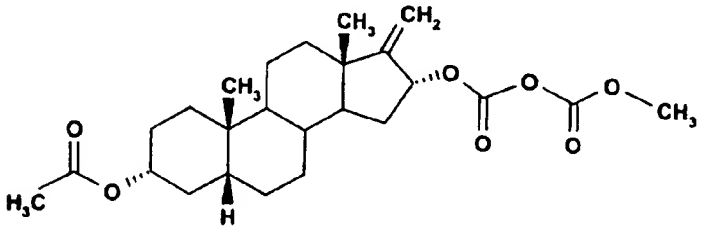


2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2-yl)ethyl 2-(6-methoxy-2-naphthyl)propionate ("Compound A");

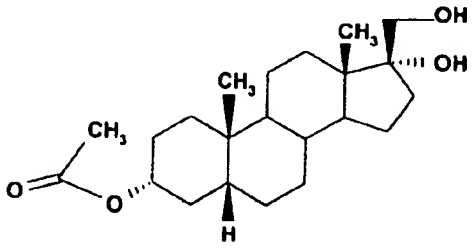
21-Nor-5ß-pregnan-3α,17α,20-triol



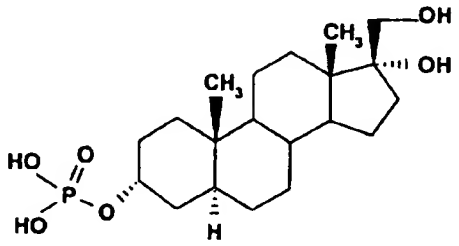
21-Nor-5ß-pregn-17(20)en-3α,16-diol-3-acetate-16-(O-methyl)malonate



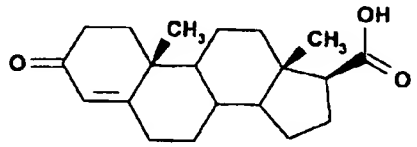
21-Nor-5ß-pregnan-3α,17α,20-triol-3-acetate



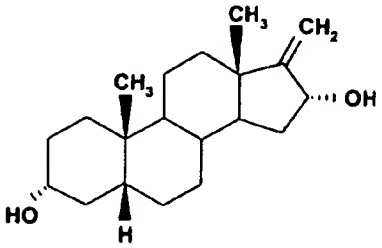
21-Nor-5α-pregnan-3α,17α,20-triol-3-phosphate



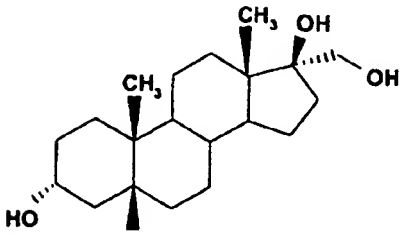
4-Androsten-3-one-17ß-carboxylic acid



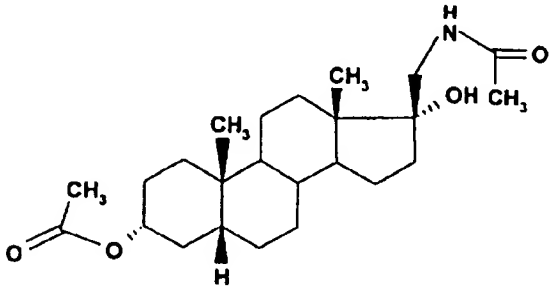
21-Nor-5ß-pregn-17(20)en-3α,16-diol



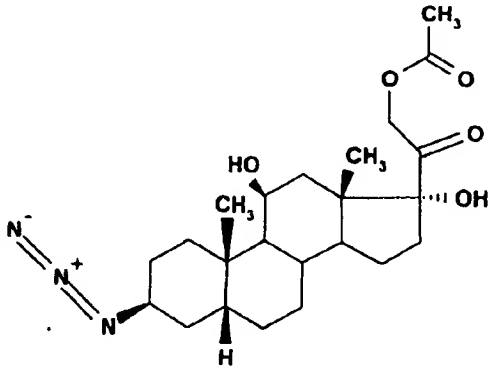
21-Nor-5ß-pregnan-3α,17 ß,20-triol



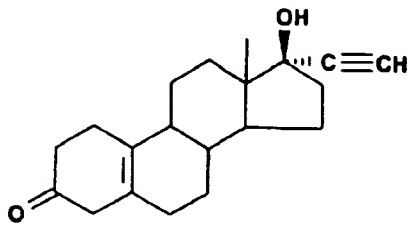
20-Acetamido-21-nor-5ß-pregnan-3α,17α-diol-3-acetate



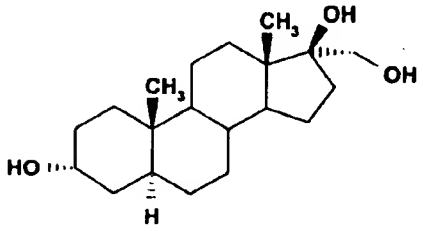
3ß-Azido-5ß-pregnan-11 ß,17α,21-triol-20-one-21-acetate



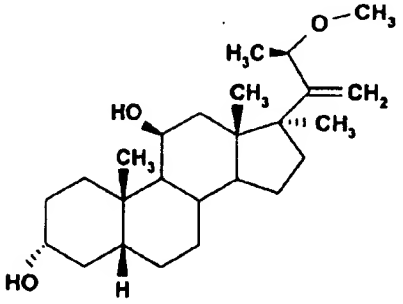
17α-Ethynyl-5(10)-estren-17ß-ol-3-one



21-Nor-5α-pregnan-3α,17ß,20-triol



21α-Methyl-5ß-pregnan-3α,11ß,17α,21-tetrol-20-one-21-methyl ether



Additionally the combinations of angiostatic agents are useful in treating pterygium (primary and recurrent), glaucoma filtration surgery bleb failure, hyperkeratosis, cheloid formation and polyp formation.

The use of the compositions of the present invention to ameliorate complications arising from glaucoma filtration surgery is a particularly important aspect of the invention. Glaucoma filtration surgery involves the surgical creation of a fistula with a conjuctival flap which allows the direct drainage of aqueous humor from the anterior chamber into the conjuctival tissue thereby lowering the elevated intraocular pressure associated with glaucoma. However, in many patients, the filtration "bleb" becomes scarred or healed over so that aqueous drainage can no longer occur. It has been noted that failing filtration blebs may become vascularized prior to failure. This vascularization may feed the fibroblasts which migrate, and proliferate, and block the bleb, or the vascularization itself may also result in physical blockage of the bleb. It is therefore likely that inhibition of filtration bleb neovascularization may inhibit filtration bleb failure.

The angiostatic compounds may be contained in various types of pharmaceutical compositions, either together as a single composition or in separate compositions, in accordance with formulation techniques known to those skilled in the art. For example, the compounds may be included in tablets, capsules, solutions, suspensions and other dosage forms adapted for oral administration; solutions and suspensions adapted for parenteral use; solutions, suspensions or gels for topical ocular administration; solutions and suspensions adapted for intra-vitreal or intra-cameral use; and suppositories for rectal use. Solutions, suspensions and other dosage forms adapted for topical application to the

solution is described in United States Patent No. 4,550,022 (Garabedian, et al.), the entire contents of which are hereby incorporated in the present specification by reference.

The specific type of formulation selected will depend on various factors, such as the compound or its salt being used, the dosage frequency, and the disease being treated. Topical aqueous solutions, suspensions, ointments, creams and gels are the preferred dosage forms for the treatment of pterygium, hyperkeratosis, and cheloid and polyp formation. Topical ophthalmic formulations are suitable for preventing glaucoma filtration bleb failure or scar formation associated with ophthalmic surgery.

In general, the doses used for the above described purposes will vary, but will be in an effective amount to inhibit or reduce neovascularization. As used herein, the term "pharmaceutically effective amount" to inhibit or reduce neovascularization, is that amount of a combination of two or more compounds of the present invention which inhibits formation of new blood vessels or reduces the number of blood vessels which are involved in the pathological condition. The compounds will normally be contained in these formulations in an amount from about 0.01 to about 10.0 weight/percent. Preferable concentrations range from about 0.1 to about 5.0 weight/percent. Thus, for topical administration, these formulations are delivered to the disease site one to six times a day, depending on the routine discretion of the skilled clinician. Systemic administration, for example, in the form of tablets or suppositories is useful for the treatment of polyp formation. Tablets containing 10-1000 mg of a compound can be taken 2-3 times per day depending on the discretion of the skilled clinician.

The compositions of the present invention are further illustrated by the following examples. The term "angiostatic compound" refers to any compound of the present invention, as described above.

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Example 1

Topical combination compositions useful for controlling ocular neovascularization:

Component	wt.%
Angiostatic Compound	0.005-5.0
Angiostatic Compound	0.005-5.0
Tyloxapol	0.01-0.05
HPMC	0.5
Benzalkonium Chloride	0.01
Sodium Chloride	0.8
Edetate Disodium	0.01
NaOH/HCl	q.s. pH 7.4
Purified Water	q.s. 100 mL

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Example 4

Formulation for sterile intraocular injection:

Component	each mL contains:
Angiostatic Compound	10-100 mg
Angiostatic Compound	10-100 mg
Sodium Chloride	7.14 mg
Potassium Chloride	0.38 mg
Calcium chloride dihydrate	0.154 mg
Magnesium chloride hexahydrate	0.2 mg
Dried sodium phosphate	0.42 mg
Sodium bicarbonate	2.1 mg
Dextrose	0.92 mg
Hydrochloric acid or sodium hydroxide	q.s., pH to approx. 7.2
Water for injection	q.s.

layer was separated, dried (Na_2SO_4), and concentrated in vacuo, resulting in a residue. A 1 M ethereal solution of hydrochloride was then added to a solution of the residue in ethyl ether (100 mL), a solid formed, and the solid was then collected by filtration and washed with ethyl ether to give 2.31 g (65.4% yield) of a white solid. The product was used crude in the next reaction.

1H-NMR (DMSO-d_6/TMS): 1.15 (s, 3H), 1.75 (t, 2H), 1.99 (s, 6H), 2.01 (s, 3H), 2.54 (t, 2H), 2.98 (s, 2H).

MS (CI): 236 (m+1).

The hydrochloride salt of (6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzo[1,2-b]pyran-2-yl)methylamine (0.30 g, 1.10 mmole) and 6-methoxy-α-methyl naphthaleneacetic acid (Aldrich, 0.28 g, 1.21 mmole) were stirred in the presence of dimethylaminopyridine (Aldrich, 0.26 g, 2.20 mmole) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Janssen Chimica-Spectrum, 0.21 g, 1.10 mmole), in tetrahydrofuran (4.0 mL) under an atmosphere of nitrogen. After stirring 17 hours at ambient temperature, the reaction mixture was diluted with ethyl acetate (70 mL), washed with water (2x 15 mL), followed by brine (15 mL) and then dried (sodium sulfate). The mixture was concentrated in vacuo and the residue subjected to flash chromatography (silica gel, 100-50:0-50, v:v, hexanes:ethyl acetate). The appropriate fractions were concentrated in vacuo, and the resulting crystalline foam suspension was then washed in hexanes to give 0.28 g (58.3% yield) of N-[(5-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-2-(6-methoxy-2-naphthyl)propionamide as a white amorphous solid.

^{1}H-NMR ($CDCl_3$) d 1.03-1.08 (d,3H), 1.57-1.64 (m, 6H), 1.70 (t, 2H,), 2.04-2.05 (m, 6H,), 2.48-2.51 (m, 2H), 3.16-3.58 (m, 2H), 3.74 (q, 1H), 3.91 (s, 3H), 4.91 (br s, 1H), 5.751 (t, 1H), 7.01-7.19 (m, 2H), 7.29-7.40 (t, 1H), 7.52-7.81 (m, 3H).

Elemental Analysis: Calculated for $C_{28}H_{33}NO_4$

Calculated: C, 75.14; H, 7.43; N, 3.13.

Found: C, 75.04; H, 7.50; N, 2.97.

Melting point: 67-70°C.

Example 12

Synthesis of 2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2yl)ethyl 2-(6-methoxy-2-naphthyl)propionate

A solution of 1,3-dicyclohexylcarbodiimide (Aldrich, 0.89 g, 4.31 mmol) in acetonitrile (25 mL), was added dropwise to a stirring slurry of (+)-6-methoxy-a-methyl-2-naphthaleneacetic acid (Aldrich, 0.90 g, 3.91 mmol), 2-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2yl)ethanol (0.98 g, 3.91 mmol, USP 5,266,709 column 45) and 1-hydroxybenzotriazole hydrate (Aldrich, 0.59 g, 4.31 mmol), in acetonitrile (50 mL). After stirring for 18 hours, the reaction mixture was concentrated in vacuo. The residue was partitioned between water (30 mL) and methylene chloride (30 mL). The layers were separated, and the aqueous layer was extracted with methylene chloride (2 x 20 mL). The combined organic extracts were washed with water (20 mL), then dried (magnesium sulfate) and concentrated in vacuo. Flash chromatography (silica gel, 2:8, v:v, ethyl acetate:hexanes) of the residue afforded a white solid upon the concentration of the appropriate fractions. The white solid was recrystallized from an ethyl acetate-hexanes mixture to give 0.60 g (33.1% yield) of 2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2yl)ethyl 2-(6-methoxy-2-naphthyl)propionate, a mixture of diastereomers, as a white solid.

^{1}H NMR ($CDCl_3$) d 1.1 (d, 3H), 1.6-1.5 (m, 3H), 1.6 (m, 2H), 1.9 (m,2H). 2.0 (s, 6H), 2.1 (s, 3H), 2.4 (t, 2H), 3.8 (q, 2H), 3.9 (s, 3H), 4.2 (s, 1H), 4.1-4.4 (m, 2H), 7.1-7.7 (m,6H).

Elemental Analysis: Calculated for $C_{29}H_{34}O_5$

Calculated: C, 75.30; H, 7.41.

Found: C, 75.24; H, 7.46.

Melting Point: 99.5-101.5°C.

afford 0.91 g (36% yield) of 2-6-hydroxy-2,5,7,8-tetra methyl-,4-dihydro-H-benzo[1,2-b]pyran-yl)ethyl 2-(3-fluoro-4-phenyl-phenyl) propionate as a mixture of stereoisomers.

^{1}H NMR ($CDCl_3$) d: 1.22-1.23 (m, 3H), 1.51-1.55 (m, 3H), 1.65-1.8 (m, 2H), 1.85-2.00 (m, 2H), 2.08 (s, 6H), 2.14 (s, 3H), 2.57 (t, 2H), 3.75 (q, 1H), 4.1-4.5 (m, 2H), 7.10-7.65 (m, 8H).

Elemental Analysis: Calculated for $C_{30}H_{33}FO_4$.
Calculated: C,75.60; H, 6.98.
Found: C,75.69; H,7.01.
Melting point: 85-87°C.

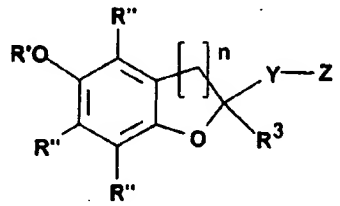
Other angiostatic compounds of the present invention are known to those skilled in the art. These compounds may be obtained by commercial sources, or synthesized by methods described in the respective publications incorporated herein or listed above.

The invention in its broader aspects is not limited to the specific details shown and described above. Departures may be made from such details within the scope of the accompanying claims without departing from the principles of the invention and without sacrificing its advantages.

What is claimed is:

1. A method of treating pathological neovascularization which comprises administering to a human a pharmaceutically effective amount of a combination of two or more angiostatic compounds.

2. A method according to Claim 1 wherein the angiostatic compounds are selected from the group consisting of: anti-mitotics, estrogen metabolites, matrix metalloproteinase inhibitors, plasminogen activator/urokinase inhibitors, urokinase receptor antagonists, platelet factor 4 and analogs, heparinases, cartilage-derived inhibitor of angiogenesis, thrombospondin and related analogs, angiostatin, vasculostatin, proliferin-related protein, fumagillin-type compounds, tecogalan, pentosan polysulfate, thalidomide and related analogs, CM101, tyrosine kinase inhibitors, anti-sense oligonucleotides, suramin-type compounds, angiostatic steriods, $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin antagonists, cytotoxic antibodies against endothelial cell antigens, interferon, VEGF and bFGF antagonists, flk-1 and flt-1 antagonists, IL-1 and TFN antagonists, and a compound according to formula (I):



(I)

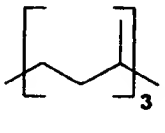
wherein:

n is 1 or 2;

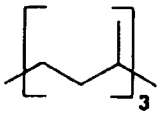
R is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R" is H or C_1-C_6 alkyl;

R^3 is H, C_1-C_6 alkyl, $(CH_2)_q(OH)$, ---$(C=O)O(CH_2)_qCH_3$ or



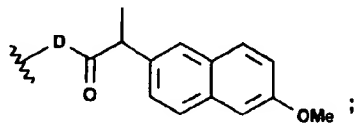
; provided that R' can not be H, when R^3 is



;

q is 1 to 10; and

Z, if present, is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or selected from the group consisting of:



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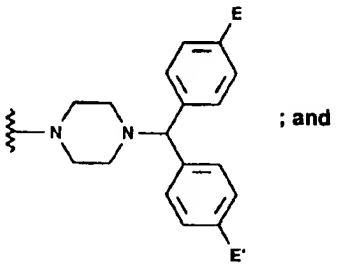
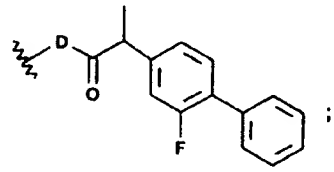


; and



;

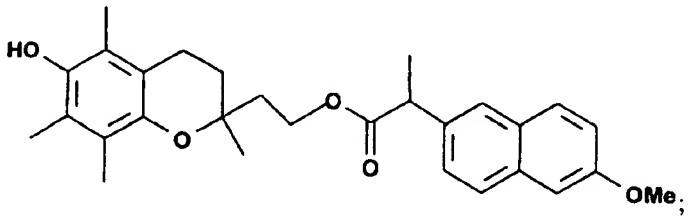
wherein:

D is O or NR; and

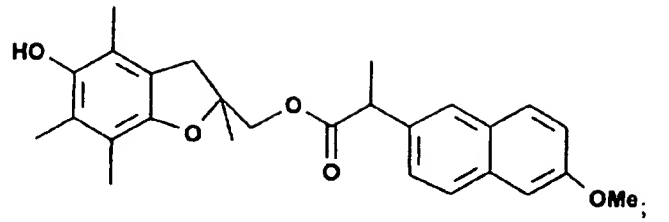
E and E' are independently H, F or Cl; and pharmaceutically acceptable salts thereof.

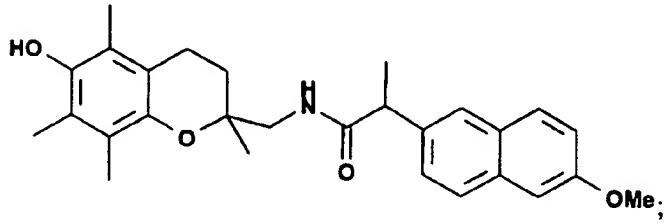
17. A composition according to Claim 15, wherein: R is H, R' is H; R" is CH_3; R^3 is CH_3; and Y is C_1-C_2 alkyl.

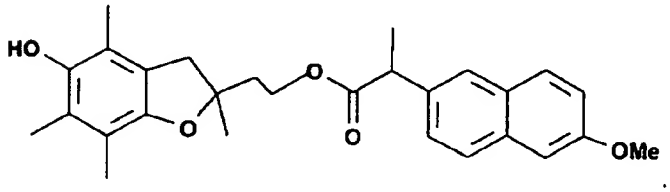
18. A composition according to Claim 15, wherein one of the compounds is selected from the group consisting of:



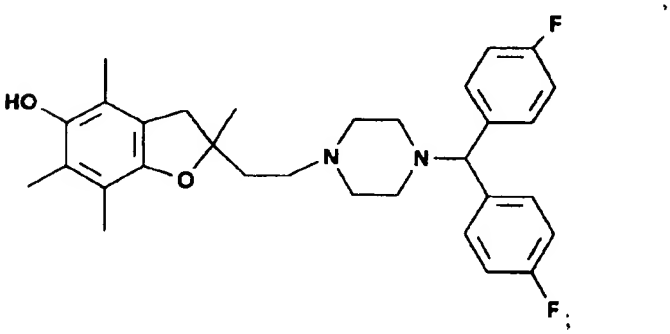
;

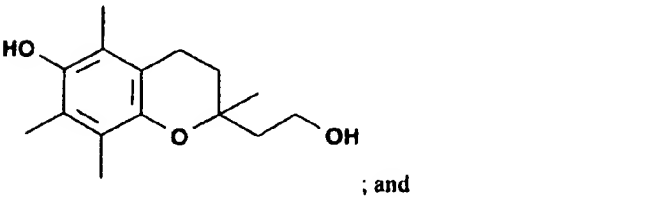




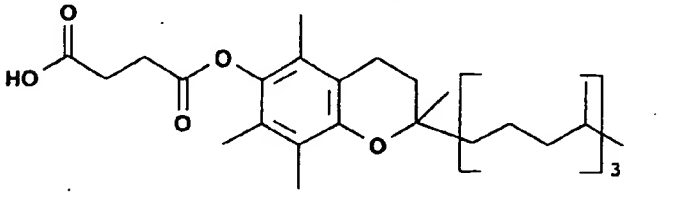


;





; and



19. A composition according to Claim 15, wherein the composition is a topical ophthalmic formulation.

20. A composition according to Claim 16, wherein the composition is a topical ophthalmic formulation.

21. A composition according to Claim 15, wherein the composition is a surgical irrigating solution.

22. A composition according to Claim 16, wherein the composition is a surgical irrigating solution.

23. A composition according to Claim 15, wherein the compounds comprise an angiostatic steroid and a compound of formula (I).

24. A composition according to Claim 15, wherein the compounds comprise a suramin-type compound and a compound of formula (I).

25. A composition according to Claim 15, wherein the compounds comprise a fumagillin-type compound and a compound of formula (I).

26. A composition according to Claim 15, wherein the compounds comprise an angiostatic steroid and a fumagillin-type compound.

27. A composition according to Claim 15, wherein the compounds comprise an angiostatic steroid and a suramin-type compound.

29. A composition according to Claim 15, wherein the compounds comprise an anti-mitotic and compound of formula (I).

INTERNATIONAL SEARCH REPORT

Inte. nal Application No
PCT/US 97/05574

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00 A61K31/34 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 90 15816 A (THE UPJOHN COMPANY) 27 December 1990 cited in the application see claims 1,2,12,13 ---	15,16,27
X	DATABASE WPI Week 9403 Derwent Publications Ltd., London, GB; AN 94-022828 XP002034658 & JP 05 331 070 A (TAKEDA CHEM IND LTD) , 14 December 1993 see abstract ---	15,16
X	WO 92 02240 A (REPLIGEN CORPORATION) 20 February 1992 see page 23, line 10 - line 23; claims 1,2 --- -/--	15,16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 July 1997	31.07.97

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)